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Pediatrics 2009;123;207-213
DOI: 10.1542/peds.2008-0338

ARTICLE

Neurodevelopmental Outcome of Extremely Low Birth Weight Infants Randomly Assigned to Restrictive or Liberal Hemoglobin Thresholds for Blood Transfusion

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The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

ELBW infants frequently need blood transfusion for anemia of prematurity. We previously published short-term outcomes of a randomized trial that showed no difference in death or major morbidity with restrictive or liberal transfusion regimens.

What This Study Adds

Follow-up of ELBW infants previously assigned to restrictive versus liberal blood transfusion regimens shows no significant difference in composite major outcome (death or neurodevelopmental impairment) at 18 to 21 months' corrected age. A posthoc analysis may favor a liberal strategy.

ABSTRACT

BACKGROUND AND OBJECTIVE. Extremely low birth weight infants frequently receive red cell transfusions. We sought to determine whether a restrictive versus liberal hemoglobin transfusion threshold results in differences in death or adverse neurodevelopmental outcomes of extremely low birth weight infants.

PATIENTS AND METHODS. Extremely low birth weight infants previously enrolled in the Preterm Infants in Need of Transfusion Trial, a randomized, controlled trial of low versus high hemoglobin transfusion thresholds, were followed up at 18 to 21 months' corrected age. Erythrocyte transfusion was determined by an algorithm of low (restrictive) or high (liberal) hemoglobin transfusion thresholds, differing by 10 to 20 g/L and maintained until first hospital discharge. The primary composite outcome was death or the presence of cerebral palsy, cognitive delay, or severe visual or hearing impairment.

RESULTS. Of 451 enrolled infants, the primary outcome was available in 430. There was no statistically significant difference in the primary outcome, found in 94 (45%) of 208 in the restrictive group and 82 (38%) of 213 in the liberal group. There were no statistically significant differences in preplanned secondary outcomes. However, the difference in cognitive delay (Mental Development Index score < 70) approached statistical significance. A posthoc analysis with cognitive delay redefined (Mental Development Index score < 85) showed a significant difference favoring the liberal threshold group.

CONCLUSIONS. Maintaining the hemoglobin of extremely low birth weight infants at these restrictive rather than liberal transfusion thresholds did not result in a statistically significant difference in combined death or severe adverse neurodevelopmental outcome. *Pediatrics* 2009;123:207–213

APPROXIMATELY 1100 INFANTS born in Canada in 2004 were <1000 g birth weight.[1] Despite recent improvements in outcomes, these infants suffer a very high mortality (~30%), and the survivors will experience high rates of neurosensory or neuromotor impairment (20%–30%).[2,3] Follow-up studies in several countries of extremely low birth weight (ELBW) infants have shown growth,[4–6] learning,[7,8] and behavioral problems[6,9] in later life.

www.pediatrics.org/cgi/doi/10.1542/peds.2008-0338

doi:10.1542/peds.2008-0338

Drs Whyte, Kirpalani, and Asztalos were coprincipal investigators; Prof Roberts had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data.
This trial has been registered at www.controlled-trials.com/isrctn (identifier 72553588).
Dr Kirpalani's current affiliation is Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA.

Key Words
extremely low birth weight, blood component transfusion, long-term, follow up, neurocognitive function, randomized, controlled trial

Abbreviations
ELBW—extremely low birth weight
PINT—Premature Infants in Need of Transfusion
MDI—Mental Development Index
GMFCS—Gross Motor Function Classification System
OR—odds ratio
CI—confidence interval

Accepted for publication Apr 15, 2008

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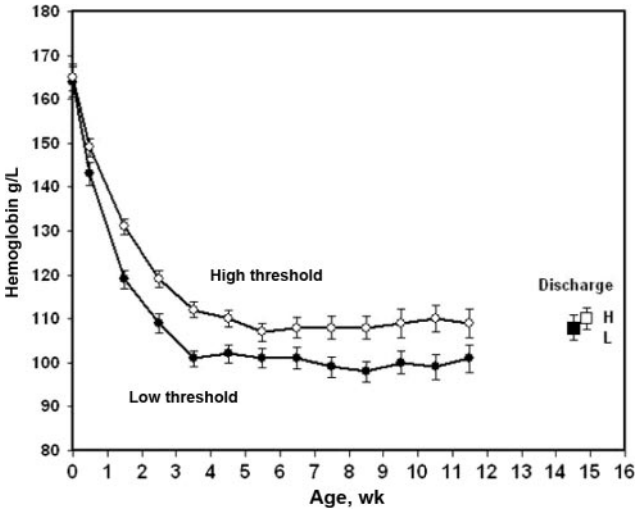

FIGURE 1.
Hemoglobin levels by postnatal age according to cohort assignment. (Reproduced with permission from Kirpalani H, Whyte RK, Anderson C, et al. *J Pediatr*. 2006;149(3):304.)

Transfusion of packed red cells is a major component of neonatal care of the very small, preterm infant. Although the frequency of blood transfusion has fallen in larger low birth weight infants, 95% of ELBW infants will receive at least 1 transfusion.[10,11] As an early intensive care intervention, blood transfusion is often characterized as an acute life-saving measure; however, in later management it may be given with a view to addressing the longer term needs of growth, development, and nutrition.

The risks and benefits of transfusion include those of maintaining high or low hemoglobin and some additional risks and benefits of the transfusion itself.[12–14] Maintaining a high hemoglobin level increases systemic oxygen transport to the tissues, but this will not usually affect oxygen uptake[15]; the lower hemoglobin levels adequate for optimal achievement of growth are undefined. We have evaluated the consequences of maintaining ELBW infants at relatively high versus relatively low hemoglobin levels in a randomized, controlled trial (Preterms In Need of Transfusion, the PINT study). The intervention achieved a mean separation of 11 g/L mean difference in hemoglobin for the first 12 weeks, which was no longer present when the infants were discharged at 15 to 16 weeks (Fig 1); however, there was no significant difference in the number of transfusions received. The short-term results in PINT[16] showed little evidence of a treatment effect on the primary neonatal outcome of death or major morbidity (defined as retinopathy of prematurity, chronic lung disease, and ultrasound findings of white matter injury) at discharge from hospital.

One other trial[17] has evaluated similar strategies of blood transfusion in the first-admission outcomes of a group of very low birth weight infants, but there are no previous trials reporting longer term outcomes. We describe here the longer-term functional outcomes of infants randomized in the PINT trial. We sought to determine whether ELBW infants maintained at restrictive (relatively low hemoglobin) versus liberal (relatively high hemoglobin) transfusion thresholds differed with respect to a combined outcome of death or neurodevelopmental impairment at 18 months' corrected age.

METHODS

Participants

Eligible infants were of birth weight <1000 g, gestational age <31 weeks, and were <48 hours old at the time of enrollment. Newborns were enrolled from 10 NICUs in Canada, the United States, and Australia. Exclusion criteria were the presence of any of the following: nonviable condition, cyanotic congenital heart disease, congenital anemia, acute shock, septic disseminated intravascular coagulopathy, a blood transfusion after 6 hours of life, or the anticipated use of erythropoietin.

Ethical review was conducted by individual institutional research ethics boards. Parental or guardian consent was separately obtained for the follow-up component of this trial. An additional and separate consent was requested for the bloodwork.

Trial Intervention

The intervention design and maneuver of PINT were described previously.[16] Infants enrolled in PINT were randomly allocated to a protocol of either low or high transfusion thresholds (Table 1) at or below which transfusion was indicated. The thresholds were specified by postnatal age and the need for respiratory support.[16] Transfusions were given as 15 mL/kg of packed red cells. The intervention was not blinded. The infant's allocated

TABLE 1 **Transfusion Thresholds in Low (Restrictive) and High (Liberal) Protocols**

Age, d	Blood Sampling	Hemoglobin, g/L			
		Low (Restrictive) Threshold		High (Liberal) Threshold	
		Respiratory Support	No Support	Respiratory Support	No Support
1–7	Capillary	≤115	≤100	≤135	≤120
	Central	≤104	≤90	≤122	≤109
8–14	Capillary	≤100	≤85	≤120	≤100
	Central	≤90	≤77	≤109	≤90
≥15	Capillary	≤85	≤75	≤100	≤85
	Central	≤77	≤68	≤90	≤77

(Reproduced with permission from Kirpalani H, Whyte RK, Anderson C, et al. *J Pediatr*. 2006;149(3):302.)

neonatal transfusion algorithm was not made known to the follow-up assessor.

Outcomes

The children were assessed at 18 to 21 months' corrected age. Centers scheduled visits as early as possible in this interval and completed missing assessments beyond the protocol-defined window only if necessary. Outcome assessments were conducted by physicians specializing in neonatal follow-up examination and certified psychologists. Neurodevelopmental follow-up was assessed by the measurement of all components of the Bayley Scales of Infant Development-II[18] from which the Mental Developmental Index (MDI) was selected for evaluation of cognitive function. A general history and physical and neurologic examinations were used to determine the presence of cerebral palsy. The Gross Motor Function Classification System (GMFCS)[19,20] was used for the functional assessment of cerebral palsy. Other outcomes included the Vineland Adaptive Behaviour Scale,[21] a visual and hearing assessment, and, where consent was available, a blood sample for hemoglobin and serum ferritin.

The primary outcome was a composite of death or neurodevelopmental impairment in survivors at 18 months' corrected age, where neurodevelopmental impairment was defined as 1 or more of the following: cerebral palsy, cognitive delay, visual or hearing impairment, as determined by the methods described.

Cerebral palsy was determined by clinician physical and neurologic examination. Cerebral palsy was diagnosed if the child had a nonprogressive motor impairment characterized by abnormal muscle tone and impaired range or control of movements. Severe or nonambulatory cerebral palsy consists of levels IV to V in the GMFCS. Cognitive delay was defined as a Bayley Scales of Infant Development-II MDI below 70 (ie, >2 SDs below age norm).[18] Severe visual impairment, determined by pediatric ophthalmologists, was defined as the best corrected vision in the better eye of visual acuity of <20/200. Hearing impairment was defined as a hearing loss requiring amplification or the insertion of a cochlear implant as determined by a soundfield hearing assessment or auditory brainstem responses.

The primary outcome was present if 1 or more of the individual components of the composite outcome was known to be present, or absent if all components were known to be absent. If no component was present, 1 or more missing components caused the primary outcome to be deemed missing.

Secondary outcomes were the individual components of the composite primary outcome, as well as personal and social function skills, gross motor function skills, measures of growth, and hematologic measures. Personal and social functions were evaluated by the Vineland Adaptive Behaviour Scale.[21] Growth was characterized as length, weight, and head circumference.

Sample Size

The sample size of the initial PINT study was 451 based on neonatal outcome rates; no additional recruitment was undertaken for this follow-up phase. We assumed that PINT infants would experience a similar rate of death or impairment to that observed in the recently completed randomized trial of prophylactic indomethacin (47%).[22] Based on this rate, we calculated that we would be able to detect with 80% power a relative risk reduction of 29% (an absolute difference of 13%) assuming 95% of the PINT infants were successfully assessed at the 18-month follow-up.

Statistical Methods

Analyses of the composite primary outcome and its components were adjusted for birth weight stratum and center by using a logistic-regression model and conducted on intention-to-treat principles without imputation for missing data. Risk difference was adjusted for center and by stratum by using a Woolf-type precision weighted approach.[23] Results for secondary outcomes have been presented as unadjusted means or proportions and P values computed via t tests or χ^2. The statistical software used was SAS 9.1.[24]

RESULTS

Recruitment

PINT trial accrual started in February 2001 and ended in February 2003. Accordingly, follow-up examinations started in November 2003 and ended in November 2005.

Completeness of Follow-up

Patient allocation and flow through the study is shown in Fig 2. Of the 451 enrollees in the original study, 88 infants died in hospital, and 363 were discharged alive, of whom 5 died before follow-up and 21 were lost to follow-up. These losses were primarily in 1 center where contact was limited by a somewhat conservative interpretation of the U.S. Health Insurance Portability and Accountability Act. Four hundred thirty infants (95%) were either known to have died before 18 months' corrected age or were seen at follow-up and were thus potentially available for analysis of the primary outcome. We were unable to complete assessment in 9 infants for whom we could not fully ascertain the presence or absence of 1 or more components (most often cognitive delay) of the more compliant-dependant assessments. There was therefore a slight variation in denominators for the separate analyses of the individual components of the primary outcome. We were able to report the full primary outcome in 421 or 93% of all infants enrolled.

Baseline Data

There were no significant differences in baseline characteristics between treatment groups for the 421 infants in whom the primary outcome status was known (Table 2). Mean (SD) birth weight was 769 (141) g, and gestational age was 26 (2) weeks.

Outcomes and Estimation

Primary Outcome and Components

Death or neurodevelopmental impairment was observed in 94 (45.2%) of 208 infants in the low hemoglobin

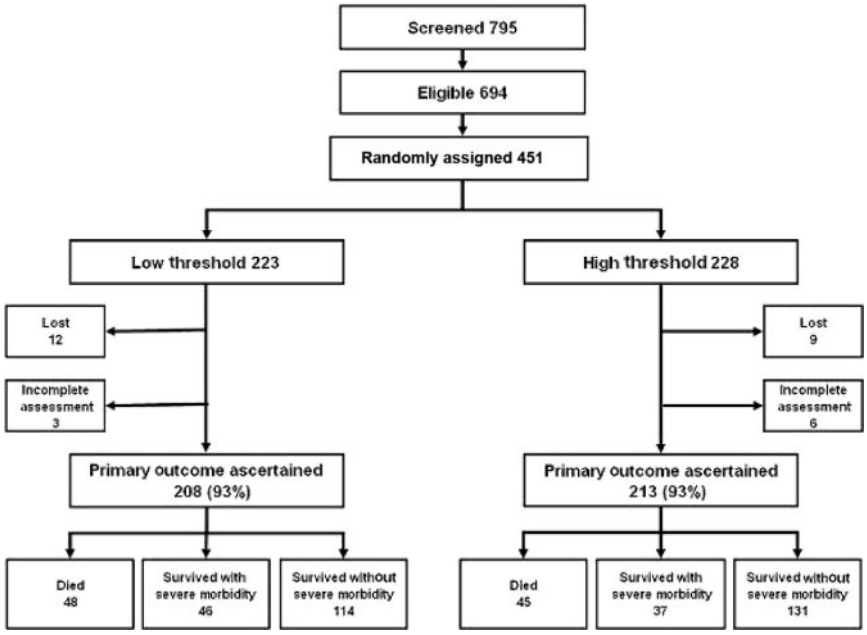

FIGURE 2.
Flow diagram of infants studied. Details of enrollment were described in a previous report.[16]

TABLE 2 **Baseline Data and Follow-up Age for Infants**

Variable	Hemoglobin Threshold	
	Low ($N = 208$)	High ($N = 213$)
Birth weight, g, mean (SD)	769 (140)	769 (142)
Gestational age, wk, mean (SD)	26 (2)	26 (2)
≤24 wk, *n* (%)	45 (22)	39 (18)
25–26 wk, *n* (%)	91 (44)	97 (46)
≥27 wk, *n* (%)	72 (35)	77 (36)
Antenatal steroids, *n* (%)	178 (86)	186 (87)
Placental abruption, *n* (%)	40 (19)	36 (16)
Cesarean section, *n* (%)	121 (58)	131 (62)
SNAP II score, mean (SD)	16 (13)	17 (13)
Male, *n* (%)	103 (49)	102 (48)
Age at follow-up, mean (SD), mo		
Chronological	22.3 (1.7)	22.3 (3.0)
Corrected	19.3 (1.7)	19.2 (3.0)

Data are confined to the 421 infants of known outcome.

threshold group versus 82 (38.5%) of 213 in the high group (Table 3). The estimated treatment effect (adjusted for center and birth weight stratum) carried an odds ratio (OR) of 1.45 (95% confidence interval [CI]: 0.94 to 2.21; the corresponding adjusted absolute difference was 3.5% (95% CI: −3.9% to 10.9%). Although not conventionally significant, this observed treatment difference has a *P* value of .091 in favor of the high group. When analyzed separately as secondary outcomes, the small observed difference in mortality and the differences of the rates of individual neurosensory impairments in survivors each favored the high group, although none of these comparisons attained statistical significance.

Other Secondary Outcomes

There were no statistically significant differences in measures of personal and social functional skills as measured by the Vineland Adaptive Behaviour Scales or in the Gross Motor Function Classification System scores (Table 4). In particular, there were similar numbers of infants categorized in the more severely dysfunctional categories (≥2; OR: 1.47 [95% CI: 0.59 to 3.57]). Weight, length, and head circumference at follow-up were not significantly different between groups (Table 5). There were no differences in mean hemoglobin, red blood cell indices, or in ferritin levels (Table 5).

Posthoc Analysis

As the outcome for the prespecified dichotomized (MDI <70) approached significance, 2 unplanned posthoc analyses were performed. A purely quantitative comparison of cognitive function resulted in a statistically significant difference in cognitive function between the infants treated with the low threshold (mean: 85.2; SD: 18.6; $n = 156$) and the high threshold (mean: 88.7; SD: 18.7; $n = 164$). This difference, after adjustment for center and birth weight stratum via multiple regression, of 4.3 points (95% CI: 0.4 to 8.2; $P = .030$) favors the high group by 0.29 SDs. Furthermore, using a 1-SD cut-point to dichotomize the MDI (as used a recently published trial in a similar population[25]) leads to rates of "cognitive delay" of 70 (44.9%) of 156 in the low group and 56 (33.9%) of 165 in the high group (adjusted OR: 1.81 [95% CI: 1.12 to 2.93]; $P = .016$). No additional analyses were conducted.

DISCUSSION

This is the first reported study, to our knowledge, comparing long-term outcomes of infants transfused to maintain high or low hemoglobin levels during early neonatal care. The allocation of infants to high or low transfusion threshold resulted in a significant difference in hemoglobin levels of ~11 g/L for the first few weeks of life, but which was no longer present at neonatal

TABLE 3 **Primary Outcome and Components of Primary Outcome**

Outcome	Hemoglobin Threshold, *n/N* (%)		OR (95% CI)	*P*
	Low	High		
Primary composite	94/208 (45.2)	82/213 (38.5)	1.45[a] (0.94–2.21)	.09
Individual components[b]				
Died[c]	48/212 (22.6)	45/219 (20.6)	1.18[a] (0.72–1.93)	.52
Any neurosensory impairment	46/160 (28.8)	37/168 (22.0)	1.62[a] (0.95–2.76)	.074
Cerebral palsy	11/163 (6.7)	9/172 (5.2)	1.32[d] (0.53–3.27)	.55
Cognitive delay	38/156 (24.4)	29/165 (17.6)	1.74[a] (0.98–3.11)	.06
Severe visual impairment	2/161 (1.2)	1/173 (0.6)	2.16[d] (0.19–24.09)	.53
Severe hearing impairment	4/161 (2.5)	3/173 (1.7)	1.45[d] (0.32–6.58)	.63

[a] Adjusted for birth weight stratum and for center. ORs are expressed as low/high.
[b] Denominators vary because some individual components were available in patients with unknown primary outcome.
[c] Of 21 infants lost to follow-up, 1 was known to be alive. This component could therefore be determined for 431 infants.
[d] Adjusted for birth weight stratum. ORs are expressed as low/high.

discharge or at follow-up at 18 months' corrected age. More importantly, there were no statistically significant differences between infants treated with high or low transfusion thresholds in the composite primary outcome, death or neurodevelopmental impairment, or in secondary outcomes at the 18-month follow-up.

We followed up infants at the earliest opportunity consistent with an adequate prediction of long-term outcome. Even with no differences in mortality between the randomized groups, the difference in hemoglobin levels or iron load may have affected neurodevelopmental outcomes. The composite primary outcome (death or cerebral palsy, cognitive delay, visual or hearing impairment) did not occur significantly more frequently in either of the groups. All of the component adverse outcomes were observed to occur more frequently in the lower transfusion threshold group: this can be attributed to these outcomes being otherwise related to each other. Mortality and cognitive delay were the most frequently occurring components in the primary cluster with the latter contributing most to the statistically modest observed difference. The secondary comparison for the component of cognitive delay approached statistical significance (OR: 1.7; $P = .06$); however, this is a supportive analysis, and the *P* value was not adjusted for the multiple tests resulting from separately comparing each individual component of the primary outcome. Posthoc analyses of the quantitative MDI score (adjusted mean difference: 4.3; $P = .030$) and of cognitive delay defined as a >1 SD below the age-standardized mean (adjusted OR: 1.8; $P = .016$) lends some plausibility to the presence of a true treatment effect favoring the high threshold group. There were no differences in secondary outcomes addressing personal and social functional skills, or in motor function.

Concerns have been expressed that maintaining hemoglobin at lower levels would have an adverse impact on growth.[26] Such an effect was not seen in the PINT study at hospital discharge, and now at 18 months we report strikingly similar measures of length, weight, and head circumference (Table 5).

Blood transfusion is an important source of iron. Both iron deficiency[27] and iron overload[14] have been identified as risk factors for neurodevelopmental impairment.[28] All infants in the study were treated with iron supplementation recommended for recovering preterm infants. There were no significant differences in measurements of hemoglobin or iron status at follow-up.

Investigators and caretakers were not blind to the study treatments during the infants' first hospital admission. The effects of the study intervention are visible in the different hemoglobin levels obtained in the first 12

TABLE 4 **Vineland Adaptive Behavioral Scales and GMFCS Levels**

Variable	Hemoglobin Threshold		*P*
	Low	High	
Vineland, *N*[a]	161	167	
Communication	83.6 (9.4)	85.3 (10.7)	.12
Daily living	83.4 (11.7)	85.0 (9.9)	.19
Socialization	90.2 (9.2)	91.1 (9.8)	.23
Motor skills	88.6 (12.3)	89.4 (14.1)	.61
GMFCS level, *N*[b]	163	172	.44
0	137	138	
1	14	25	
2	3	2	
3	3	2	
4	3	2	
5	3	3	

[a] The values indicate standardized mean score (SD).
[b] The values indicate the number of infants.

TABLE 5 **Size and Hematologic Outcomes at Follow-up**

Variable	Hemoglobin Threshold		*P*
	Low	High	
Size, mean (SD) (*n*)			
Weight, kg	10.35 (1.78) (162)	10.35 (1.87) (170)	.96
Length, cm	79.7 (4.0) (163)	79.3 (4.3) (167)	.46
Head circumference, cm	47.2 (1.8) (160)	46.8 (2.3) (170)	.11
Hematology, mean (SD) (*n*)			
Hemoglobin, g/L	124.9 (10.6) (116)	125.7 (11.1) (114)	.88
Hematocrit fr.	0.37 (0.036) (116)	0.37 (0.031) (114)	.93
Mean corpuscular hemoglobin, g/L Concentration, g/L	321 (72) (115)	315 (81) (113)	.60
Mean cell volume, fL	88.6 (12.3) (115)	89.4 (14.1) (114)	.61
Ferritin, μmol/L	27.7 (23.5) (114)	28.0 (23.8) (110)	.90

weeks. The evaluators of the infants' follow-up status were not made aware of study allocation.

Our results are generalizable to most ELBW infants treated in NICUs. The transfusion practices compared represented the tolerable extremes of transfusion regimens practiced at the time of enrollment. Our study provides some weak evidence of benefit from a higher hemoglobin threshold for transfusion primarily through a secondary analysis of cognitive delay. Because this finding combines a protocol-defined analysis of borderline statistical significance with a posthoc analysis of both clinical and statistical significance, it is not conclusive in its own right but is hard to dismiss as simply the play of chance. We therefore advocate caution in the interpretation of these results, and call for additional investigation of the effects of transfusion regimes in the prevention of neurodevelopmental impairment in ELBW infants.

ACKNOWLEDGMENTS

This work was supported by the Canadian Institutes for Health Research registration MCT-58455.

The PINTOS Study Group includes the following: Albany Medical Center, United States: Angel Rios, MD, Anthony Malone, MD, P. Graziano, RN, BSN, Susan Boynton, RN, BSN; Brooklyn Hospital Center, United States: Meena LaCorte, MD, Patrick Leblanc, MD, A. Braithwaite, NNP; Glenrose Rehabilitation Hospital, Edmonton, Alberta, Canada: C. Robertson, MD; Kingston General Hospital, Canada: Maxine Clarke, MD; Dalhousie University and IWK Health Centre Halifax, Canada: Robin Whyte, MD, Michael Vincer, MD, Sharon Stone, RN, Heather Cake, MA; McMaster University, Hamilton, Canada: Haresh Kirpalani, MD, MSc, Morris A. Blajchman, MD, Nancy M. Heddle, MSc, Marie Kim, MD, Joanne Dix, Janice Cairnie; Melbourne Mercy for Women, Victoria, Australia: Chad Andersen MBBS, Anna Burdett; Melbourne Royal Women's Hospital, Victoria, Australia: Lex Doyle, MD, MSc, Kate Callanan, RN, Noni Davis, MB, Elaine Kelly, MA, Geoff Ford, MB; Royal Victoria Montreal, Canada: May Khairy, MD; University of Toronto and Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada: Elizabeth Asztalos, Maralyn Lacy, and Denise Hohn; Coordinating and Methods Center, Hamilton Ontario: Robin Roberts, MSc, Carole Chambers, Lorrie Costantini, MSc, Kevin Thorpe, MMath.

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Editors: Goodman, Denise M., MD, MSc; Green, Thomas P., MD; Unti, Sharon M., MD; Powell, Elizabeth C., MD, MPH
Publisher: McGraw-Hill Companies
List Price: $74.95
Reviewer: Pinar Bulut, MD (Ochsner Clinic Foundation)
Description: This illustrated guide covers virtually all procedures that a pediatrician might need to perform. Each chapter is well structured with written text accompanied by instructive illustrations. Procedures are all presented in a standard format that offers insight with risks and benefits.
Purpose: The purpose is to serve as a comprehensive review of technical medical procedures applicable to pediatric patients. This is a useful guide for those who practice in the field of pediatrics rendering either inpatient or outpatient care.
Audience: The audience includes students, residents, practitioners, and anyone who provides primary care, whether in an inpatient or outpatient setting.
Features: Procedures are discussed based on organ system with a review of anatomy, risks, complications, and indications. The simple figures are easy to comprehend. The best chapter is the one that describes common procedures that are frequently performed in daily practice. All procedures are listed and well explained. The information is delivered in a direct and easy to understand language and complemented by clear and well-done illustrations.
Assessment: This is a great first edition reference, providing guidance and step-by-step instruction for procedures in pediatrics and pediatric subspecialties. It is very useful for students and housestaff while on call and also will be of benefit to primary care providers and practitioners.

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Neurodevelopmental Outcome of Extremely Low Birth Weight Infants Randomly Assigned to Restrictive or Liberal Hemoglobin Thresholds for Blood Transfusion

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Pediatrics 2009;123;207-213
DOI: 10.1542/peds.2008-0338